Day : Thursday
Date: 11/9/2006
Time: 20:12:44

PALM INTRANET

Inventor Information for 10/813760

Inventor Name	City	State/Country
BERNSTEIN, JOEL E.	DEERFIELD	ILLINOIS

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity/Reexam | Foreign Data | Invento

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PCT / [ ] / [ ] Search **or PG PUBS #** [ ] Search

Attorney Docket # [ ] Search

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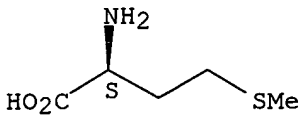
L2 ANSWER 39091 OF 39092 REGISTRY COPYRIGHT 2006 ACS on STN
RN 63-68-3 REGISTRY
ED Entered STN: 16 Nov 1984
CN **L-Methionine (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Methionine, L- (8CI)**
OTHER NAMES:
CN (S)-2-Amino-4-(methylthio)butanoic acid
CN α-Amino-γ-methylmercaptobutyric acid
CN γ-Methylthio-α-aminobutyric acid
CN 1139: PN: WO2004048938 SEQID: 1139 claimed protein
CN 2-Amino-4-(methylthio)butyric acid
CN 395: PN: US20030049618 SEQID: 395 claimed protein
CN 395: PN: US20060084082 SEQID: 395 claimed protein
CN 46: PN: WO2004076659 FIGURE: 7 claimed protein
CN Acimethin
CN Butanoic acid, 2-amino-4-(methylthio)-, (S)-
CN Cymethion
CN h-Met-oh
CN **L-(-)-Methionine**
CN L-α-Amino-γ-methylthiobutyric acid
CN L-Homocysteine, S-methyl-
CN **l-Methionine**
CN **Methionine**
CN NSC 22946
CN **S-Methionine**
CN S-Methyl-L-homocysteine
CN Secretory peptide (human clone HTXDU73)
FS STEREOSEARCH
DR 7005-18-7, 24425-78-3
MF C5 H11 N O2 S
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PATDPASPC, PIRA, PROMT, PS, RTECS*, SPECINFO, TOXCENTER, TULSA, ULIDAT, USAN, USPAT2, USPATFULL, VETU, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.

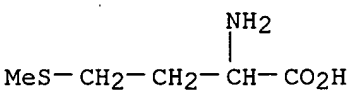


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

39048 REFERENCES IN FILE CA (1907 TO DATE)
957 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
39135 REFERENCES IN FILE CAPLUS (1907 TO DATE)
10 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L2 ANSWER 39092 OF 39092 REGISTRY COPYRIGHT 2006 ACS on STN
RN 59-51-8 REGISTRY
ED Entered STN: 16 Nov 1984
CN **Methionine (9CI)** (CA INDEX NAME)

OTHER CA INDEX NAMES:
CN **DL-Methionine**
CN **Methionine, DL- (8CI)**
OTHER NAMES:
CN **(±)-Methionine**
CN α-Amino-γ-methylmercaptobutyric acid
CN Acimetion
CN Amurex
CN Banthionine
CN Cynaron
CN DL-2-Amino-4-(methylthio)butyric acid
CN Dyprin
CN Lactet
CN Lobamine
CN Meonine
CN Meprom M 85
CN Methilanin
CN Metione
CN Neston
CN NSC 9241
CN Pedameth
CN **Racemethionine**
CN Rhodimet NP 99
CN Urimeth
MF C5 H11 N O2 S
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DETHERM*, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PIRA, PROMT, RTECS*, TOXCENTER, TULSA, ULIDAT, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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81 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3221 REFERENCES IN FILE CAPLUS (1907 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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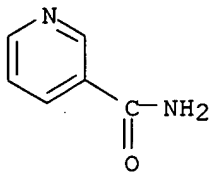
L3 ANSWER 37730 OF 37738 REGISTRY COPYRIGHT 2006 ACS on STN
RN 98-92-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Nicotinamide (8CI)**
OTHER NAMES:
CN β-Pyridinecarboxamide
CN 3-(Aminocarbonyl)pyridine
CN 3-Amidopyridine
CN 3-Carbamoylpyridine
CN 3-Pyridinecarboxylic acid amide
CN Aminicotin
CN Benicot
CN Delonin Amide
CN Dipegyl
CN m-(Aminocarbonyl)pyridine
CN NAM
CN Niacinamide
CN Niavit PP
CN Nicamina
CN Nicamindon
CN Nicasir
CN Nicobion
CN Nicofort
CN Nicosan 2
CN Nicosylamide
CN Nicotilamide
CN Nicotine acid amide
CN Nicotinic acid amide
CN Nicotinic amide
CN Nicotylamide
CN Nicovit
CN Nicovitina
CN Nictoamide
CN Niocinamide
CN Niozymin
CN NSC 13128
CN NSC 27452
CN Papulex
CN Pelmin
CN Pelmine
CN Pelonin amide
CN Vi-Nicotyl
CN Vitamin B
CN Vitamin B3
DR 123574-63-0, 37321-14-5, 78731-47-2
MF C6 H6 N2 O
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PHAR, PIRA, PROMT, PS, RTECS*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)


N
C
NH2
O

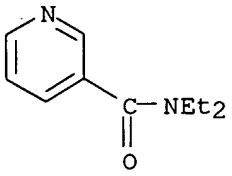
L3 ANSWER 37734 OF 37738 REGISTRY COPYRIGHT 2006 ACS on STN
RN 59-26-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN 3-Pyridinecarboxamide, N,N-diethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Nicotinamide, N,N-diethyl- (8CI)**
OTHER NAMES:
CN 3-(N,N-Diethylcarbamoyl)pyridine
CN Anacardone
CN Anacordone
CN Astrocar
CN Canfodiamina
CN Carbamidal
CN Cardamine
CN Cardiamid
CN Cardiamide
CN Cardiamine
CN Cardimon
CN Coracon
CN Coractiv N
CN Coramine
CN Coramine (pharmaceutical)
CN Cordiamin
CN Cordiamine
CN Corediol
CN Cormed
CN Cormid
CN Cormotyl
CN Cornotone
CN Corvin
CN Corvitol
CN Corvotone
CN **Diethylnicotinamide**
CN Dynacoryl
CN Ecoran
CN Eucoran
CN Kordiamin
CN N,N-Diethyl-3-pyridinecarboxamide
CN **N,N-Diethylnicotinamide**
CN Ni-Cor
CN Niamine
CN Nicamide
CN Nicetamide
CN Nicethamide
CN Nicorine
CN Nicotinic acid diethylamide
CN Nikardin
CN Niketamide
CN Niketamine
CN Nikethamide
CN Niketharol
CN Nikethyl
CN Nikorin
CN Niquetamide
CN NSC 130820
CN NSC 169863
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
MF C10 H14 N2 O
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU,

EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MEDLINE, MRCK*, PHAR, PIRA, PROMT, PS, RTECS*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL

(*File contains numerically searchable property data)

Other Sources: EINECS**, WHO

(**Enter CHEMLIST File for up-to-date regulatory information)

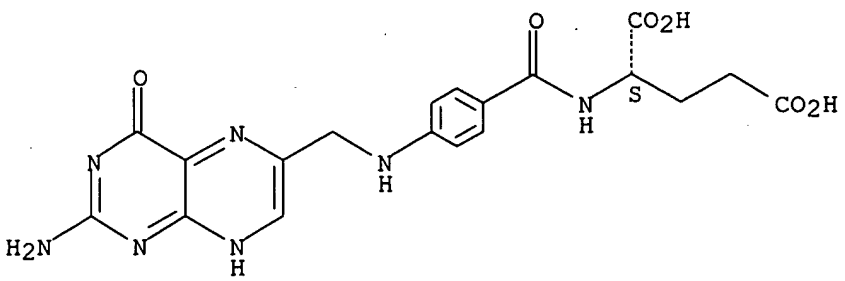


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

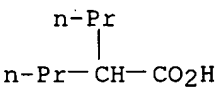
1237 REFERENCES IN FILE CA (1907 TO DATE)
34 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1237 REFERENCES IN FILE CAPLUS (1907 TO DATE)
25 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L4 ANSWER 211 OF 214 REGISTRY COPYRIGHT 2006 ACS on STN
RN 59-30-3 REGISTRY
ED Entered STN: 16 Nov 1984
CN L-Glutamic acid, N-[4-[[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Folic acid (8CI)**
OTHER NAMES:
CN Acifolic
CN Cytofol
CN Dosfolat B activ
CN Folacid
CN Folacin
CN Folbal
CN Folcidin
CN Foldine
CN Folettes
CN Foliamin
CN Folicet
CN Folipac
CN Folsan
CN Folsaure
CN Folsav
CN Folvite
CN Incafolic
CN Liver Lactobacillus casei factor
CN Millafol
CN NSC 3073
CN PGA
CN Pteroyl-L-glutamic acid
CN Pteroyl-L-monoglutamic acid
CN Pteroylglutamic acid
CN Pteroylmonoglutamic acid
CN Vitamin Bc
CN Vitamin Be
CN Vitamin M
FS STEREOSEARCH
DR 33609-88-0
MF C19 H19 N7 O6
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PIRA, PROMT, PS, RTECS*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



L20 ANSWER 17 OF 17 REGISTRY COPYRIGHT 2006 ACS on STN
RN 99-66-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN Pentanoic acid, 2-propyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Valeric acid, 2-propyl- (6CI, 7CI, 8CI)
OTHER NAMES:
CN 2-Propylpentanoic acid
CN 2-Propylvaleric acid
CN 4-Heptanecarboxylic acid
CN 44089
CN Acetic acid, dipropyl-
CN Depakine
CN Dipropylacetic acid
CN DPA
CN Ergenyl
CN Mylproin
CN n-Dipropylacetic acid
CN NSC 93819
CN **Valproic acid**
MF C8 H16 O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PROUSDDR, PS, RTECS*, SCISEARCH, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

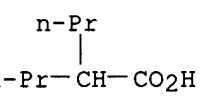


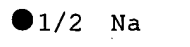
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4429 REFERENCES IN FILE CA (1907 TO DATE)
158 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
4445 REFERENCES IN FILE CAPLUS (1907 TO DATE)
7 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

L19 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN
RN 76584-70-8 REGISTRY
ED Entered STN: 16 Nov 1984
CN Pentanoic acid, 2-propyl-, sodium salt (2:1) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Abbott 50711
CN Depakote
CN **Divalproex sodium**
CN Epival
CN Sodium hydrogen bis(2-propylpentanoate)
CN Sodium hydrogen bis(2-propylvalerate)
CN Sodium hydrogen divalproate
CN Valdisoval
CN Valproate semisodium
AR 133299-66-8
MF C8 H16 O2 . 1/2 Na
CI COM
LC STN Files: ADISNEWS, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, GMELIN*, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MRCK*, PHAR, PROMT, PROUSDDR, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO
CRN (99-66-1)



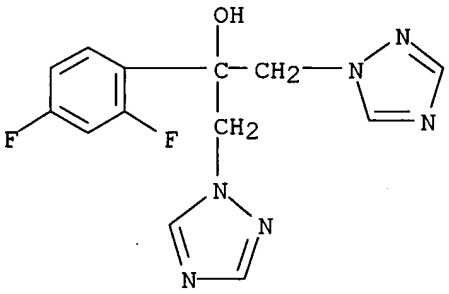


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

287 REFERENCES IN FILE CA (1907 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
289 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>

L16 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2006 ACS on STN
RN 86386-73-4 REGISTRY
ED Entered STN: 16 Nov 1984
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Biozolene
CN Diflucan
CN Elazor
CN **Fluconazole**
CN Flucostat
CN Flumycon
CN Flunazol
CN Flusol
CN Fluzon
CN Triflucan
CN UK 49858
CN Zoltec
DR 123631-92-5
MF C13 H12 F2 N6 O
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, IFICDB, IFIUDB, IMSCOSEARCH, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, PATDPASPC, PHAR, PROMT, PROUSDDR, PS, RTECS*, SCISEARCH, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: WHO



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3130 REFERENCES IN FILE CA (1907 TO DATE)
30 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3146 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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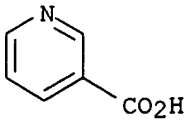
L15 ANSWER 23 OF 23 REGISTRY COPYRIGHT 2006 ACS on STN
RN 59-67-6 REGISTRY
ED Entered STN: 16 Nov 1984
CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Nicotinic acid (7CI, 8CI)
OTHER NAMES:
CN β-Pyridinecarboxylic acid
CN 3-Carboxylpyridine
CN 3-Carboxypyridine
CN 3-Pyridylcarboxylic acid
CN Akotin
CN Apelagrin
CN Daskil
CN E 375
CN Efacin
CN Enduracin
CN Linic
CN Niac
CN **Niacin**
CN Niacor
CN Niaspan
CN Nicacid
CN Nicangin
CN Nico-Span
CN Nicobid
CN Nicodelmine
CN Nicolar
CN Niconacid
CN Nicosan 3
CN Nicotinipca
CN Nicyl
CN NSC 169454
CN Nyclin
CN Pellagrin
CN Pelonin
CN **Slo-niacin**
CN SR 4390
CN Vitamin B5
CN Wampocap
DR 123574-58-3
MF C6 H5 N O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PHAR, PIRA, PROMT, PROUSDDR, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, TULSA, ULIDAT, USAN, USPAT2, USPATFULL, VETU, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

16810 REFERENCES IN FILE CA (1907 TO DATE)
786 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
16861 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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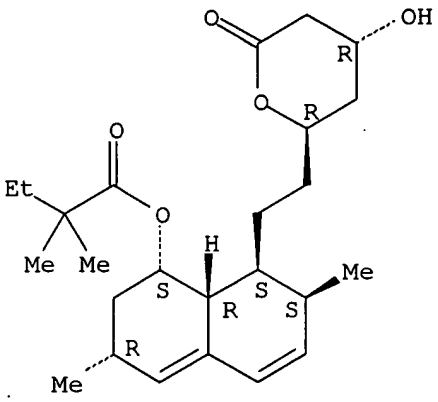
L14 ANSWER 17 OF 17 REGISTRY COPYRIGHT 2006 ACS on STN
RN 79902-63-9 REGISTRY
ED Entered STN: 16 Nov 1984
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1α,3α,7β,8β(2S*,4S*),8aβ]]-
OTHER NAMES:
CN **(+)-Simvastatin**
CN Cholestat
CN Denan
CN Eucor
CN Kolestevan
CN L 644128-000U
CN Lipex
CN Lipinorm
CN Liponorm
CN Lipovas
CN Lodales
CN MK 733
CN Modutrol
CN Nor-Vastina
CN Rechol
CN Simcor
CN Simovil
CN **Simvastatin**
CN **Simvastatin lactone**
CN Simvotin
CN Sinvacor
CN Sinvascor
CN Sivastin
CN Statin
CN Synvinolin
CN Valemia
CN Velostatin
CN Zocor
CN Zocord
FS STEREOSEARCH
DR 98609-43-9, 118607-03-7
MF C25 H38 O5
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, HSDB*, IFICDB, IFIUDB, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, NAPRALERT, PATDPASPC, PHAR, PROMT, PROUSDDR, PS, RTECS*, SCISEARCH, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.



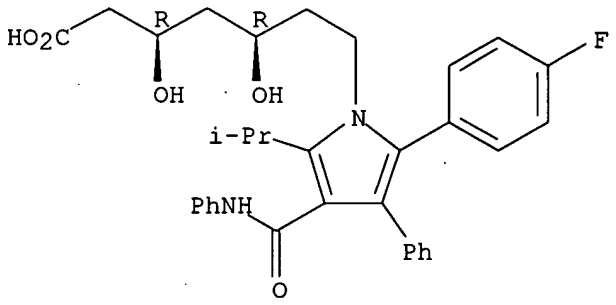
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3298 REFERENCES IN FILE CA (1907 TO DATE)
79 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3317 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>

L13 ANSWER 11 OF 12 REGISTRY COPYRIGHT 2006 ACS on STN
RN 134523-00-5 REGISTRY
ED Entered STN: 28 Jun 1991
CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, (βR,δR)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, [R-(R*,R*)]-
OTHER NAMES:
CN (βR,δR)-2-(p-Fluorophenyl)-β,δ-dihydroxy-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrole-1-heptanoic acid
CN (3R,5R)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid
CN **Atorvastatin**
CN **Atorvastatin acid**
CN Cardyl
FS STEREOSEARCH
MF C33 H35 F N2 O5
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, DDFU, DRUGU, EMBASE, HSDB*, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PATDPASPC, PROMT, PROUSDDR, PS, RTECS*, SCISEARCH, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.



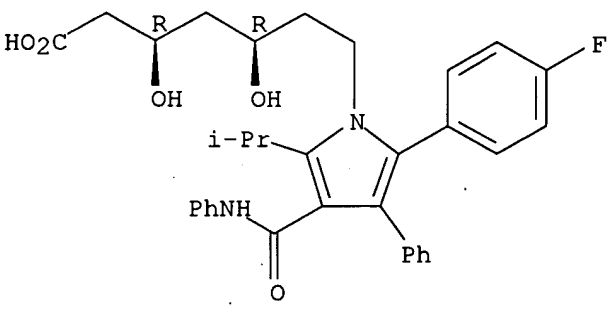
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2274 REFERENCES IN FILE CA (1907 TO DATE)
54 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2287 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>

L13 ANSWER 10 OF 12 REGISTRY COPYRIGHT 2006 ACS on STN
RN 134523-01-6 REGISTRY
ED Entered STN: 28 Jun 1991
CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, monosodium salt, (βR,δR)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, monosodium salt, [R-(R*,R*)]-
OTHER NAMES:
CN **Atorvastatin sodium**
FS STEREOSEARCH
MF C33 H35 F N2 O5 . Na
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, CHEMCATS, IMSPATENTS, IMSRESEARCH, MRCK*, USPAT2, USPATFULL
(*File contains numerically searchable property data)
CRN (134523-00-5)

Absolute stereochemistry.

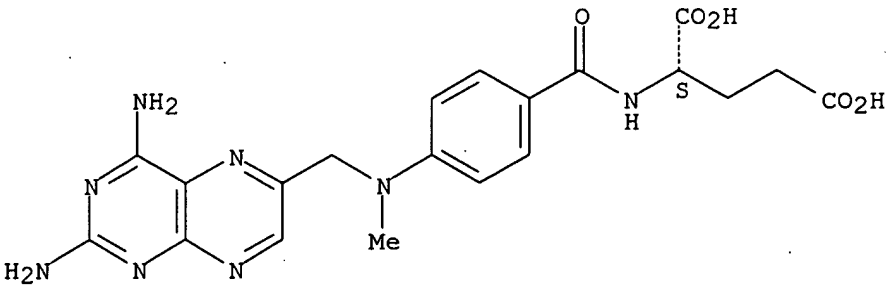


● Na

21 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
22 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L11 ANSWER 102 OF 102 REGISTRY COPYRIGHT 2006 ACS on STN
RN 59-05-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN L-Glutamic acid, N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Glutamic acid, N-[p-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-, L-(+)- (8CI)
OTHER NAMES:
CN (+)-Amethopterin
CN 4-Amino-10-methylfolic acid
CN 4-Amino-N10-methylfolic acid
CN 4-Amino-N10-methylpteroylglutamic acid
CN Amethopterin
CN Amethopterine
CN Antifolan
CN CL 14377
CN EMT 25299
CN Emtexate
CN L-Amethopterin
CN **L-Methotrexate**
CN Ledertrexate
CN Metatrexan
CN Methotrexat-Ebewe
CN **Methotrexate**
CN Methylaminopterin
CN Mexate
CN MTX
CN N-[p-[[2,4-Diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-(+)-glutamic acid
CN NSC 740
CN R 9985
CN Rheumatrex
FS STEREOSEARCH
MF C20 H22 N8 O5
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, PHAR, PROMT, PROUSDDR, PS, RTECS*, SCISEARCH, SPECINFO, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



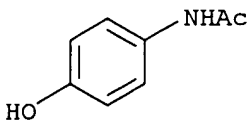
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

13482 REFERENCES IN FILE CA (1907 TO DATE)
  846 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
13538 REFERENCES IN FILE CAPLUS (1907 TO DATE)
   73 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

L10 ANSWER 132 OF 132 REGISTRY COPYRIGHT 2006 ACS on STN
RN 103-90-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetanilide, 4'-hydroxy- (7CI, 8CI)
OTHER NAMES:
CN 4'-Hydroxyacetanilide
CN 4-(Acetylamino)phenol
CN 4-(N-Acetylamino)phenol
CN 4-Acetamidophenol
CN **4-Acetaminophenol**
CN 4-Hydroxyacetanilide
CN Abensanil
CN Acamol
CN Acenol
CN Acenol (pharmaceutical)
CN Acetagesic
CN Acetalgin
CN Acetaminofen
CN **Acetaminophen**
CN Algotropyl
CN Alpiny
CN Alvedon
CN Amadil
CN Anaflon
CN Anelix
CN Anhiba
CN Apamid
CN Apamide
CN APAP
CN Banesin
CN Ben-u-ron
CN Benzenediol, 4-amino-, 2(or 3)-acetate
CN Bickie-mol
CN Biocetamol
CN Calpol
CN Captin
CN Cetadol
CN Citramon P
CN Claratal
CN Clixodyne
CN Crocin
CN Dafalgan
CN Daphalgan
CN Datril
CN Dial-a-gesic
CN Dirox
CN Disprol
CN Doliprane
CN Dolprone
CN Duorol
CN Dymadon
CN Efferalgan
CN Endophy
CN Enelfa
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
DR 719293-04-6, 8055-08-1
MF C8 H9 N O2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOSIS,

BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, PATDPASPC, PHAR, PIRA, PROMT, PROUSDDR, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

12807 REFERENCES IN FILE CA (1907 TO DATE)
280 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
12858 REFERENCES IN FILE CAPLUS (1907 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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     (FILE 'HOME' ENTERED AT 20:18:26 ON 09 NOV 2006)

     FILE 'REGISTRY' ENTERED AT 20:18:38 ON 09 NOV 2006

     FILE 'REGISTRY' ENTERED AT 20:18:54 ON 09 NOV 2006
L1             0 S FLUCANOZOLE
L2         39092 S METHIONINE
L3         37738 S NICOTINAMIDE
L4           214 S FOLIC ACID

     FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE' ENTERED AT 20:25:47 ON 09 NOV 2006
L5        225232 S 63-68-3/RN OR 59-51-8/RN OR METHIONINE
L6        149134 S 98-92-0/RN OR NICOTINAMIDE OR VITAMIN B OR NIACINAMIDE OR NIC
L7         74827 S 59-30-3/RN OR FOLIC ACID OR PTEROYLGLUTAMIC ACID OR PTEROYLMO
L8          4350 S L5 AND L6
L9          1461 S L8 AND L7

     FILE 'REGISTRY' ENTERED AT 20:28:57 ON 09 NOV 2006
L10          132 S ACETAMINOPHEN
L11          102 S METHOTREXATE
L12            0 S ATROVASTATIN
L13           12 S ATORVASTATIN
L14           17 S SIMVASTATIN
L15           23 S NIACIN
L16            4 S FLUCONAZOLE

     FILE 'REGISTRY' ENTERED AT 20:31:22 ON 09 NOV 2006
                SET TERMSET E#
                DEL SEL Y
                SEL L16 4 RN
L17             1 S E1/RN
                SET TERMSET LOGIN

     FILE 'IMSPATENTS' ENTERED AT 20:31:27 ON 09 NOV 2006
L18            94 S L17

     FILE 'REGISTRY' ENTERED AT 20:31:36 ON 09 NOV 2006
L19             1 S DIVALPROEX SODIUM
L20            17 S VALPROIC ACID

     FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE' ENTERED AT 20:32:48 ON 09 NOV 2006
L21         41259 S 103-90-2/RN OR ACETAMINOPHEN OR TYLENOL OR ACETAMINOFEN OR AP
L22         41014 S 103-90-2/RN OR ACETAMINOPHEN OR TYLENOL OR ACETAMINOFEN
L23        153836 S METHOTREXATE OR 59-05-2/RN
L24         15008 S 134523-00-5/RN OR ATORVASTATIN
L25         22400 S SIMVASTATIN OR 79902-63-9/RN
L26         16267 S 59-67-6/RN
L27         28378 S 59-67-6/RN  OR NIACIN OR 3-CARBOXYLPYRIDINE
L28         31733 S 86386-73-4/RN OR FLUCONAZOLE
L29           286 S 76584-70-8/RN OR DIVAPROEX SODIUM
L30         41615 S 99-66-1/RN OR VALPROIC ACID

=> s l21 or l22 or l23 or l24 or l25 or l26 or l27 or l28 or l29 or l30
L31        323535 L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR
                  L30

=> s l31 and l8
L32          348 L31 AND L8

=> s l31 and l9
L33          151 L31 AND L9
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=> dup rem l32
PROCESSING COMPLETED FOR L32
L34          311 DUP REM L32 (37 DUPLICATES REMOVED)

=> dup rem l33
PROCESSING COMPLETED FOR L33
L35          147 DUP REM L33 (4 DUPLICATES REMOVED)

=> s hepato? or hepatic or liver
L36     2580162 HEPATO? OR HEPATIC OR LIVER

=> s l36 and (toxic or toxicity or hepatotoxicity or damage)
L37      345852 L36 AND (TOXIC OR TOXICITY OR HEPATOTOXICITY OR DAMAGE)

=> s l36 and l37
L38      345852 L36 AND L37

=> s l34 and l38
L39          20 L34 AND L38

=> s l35 and l38
L40           7 L35 AND L38

=> focus l39 or l40
OR IS NOT VALID HERE
The term is either unrecognized or invalid.

=> focus l39
PROCESSING COMPLETED FOR L39
L41          20 FOCUS L39 1-

=> focus l40
PROCESSING COMPLETED FOR L40
L42           7 FOCUS L40 1-

=> d ibib abs hitstr 1-20 l41

L41  ANSWER 1 OF 20  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1999:524628  CAPLUS
DOCUMENT NUMBER:          131:317404
TITLE:                    Nicotinamide and methionine reduce
                          the liver toxic effect of
                          methotrexate
AUTHOR(S):                Kroger, H.; Hauschild, A.; Ohde, M.; Bache, K.; Voigt,
                          W. P.; Thefeldt, W.; Kruger, D.
CORPORATE SOURCE:         Deutsches Rheumaforschungszentrum Berlin, Berlin,
                          10115, Germany
SOURCE:                   General Pharmacology (1999), 33(2), 203-206
                          CODEN: GEPHDP; ISSN: 0306-3623
PUBLISHER:                Elsevier Science Inc.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Methotrexate is widely used as a therapeutic agent in different
     diseases.  This therapy is connected with various side effects, including
     liver toxicity.  The authors have developed a mouse
     model to demonstrate the toxic effects of methotrexate
     : mice were given 50 mg/kg acetaminophen, which itself has no
     effect on the liver.  If, addnl., methotrexate is
     applied, there is an increase in the death rate, as well as in
     glutamate-oxaloacetate transaminase (GOT) and glutamate-pyruvate
     transminase (GPT) activities.  If methotrexate is administered
     in conjunction with either nicotinamide or methionine,
     the rise in the death rate and in GOT and GPT activities associated with
```

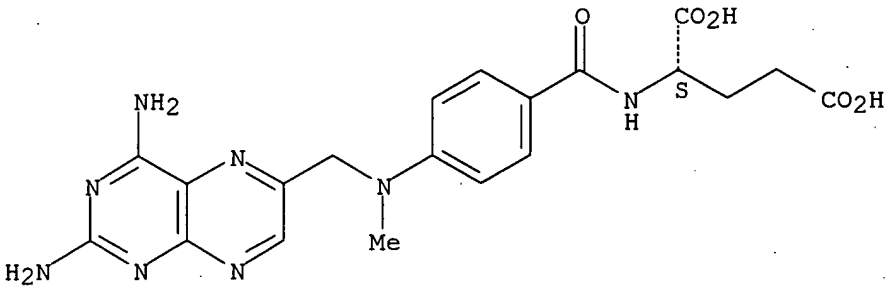
methotrexate application is markedly reduced. On the basis of these results, it can be concluded that **methotrexate** therapy should be combined with either **nicotinamide** or **methionine**, resp.

IT **59-05-2, Methotrexate**
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**nicotinamide** and **methionine** reduce **liver toxicity** of **methotrexate**)

RN 59-05-2 CAPLUS

CN L-Glutamic acid, N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

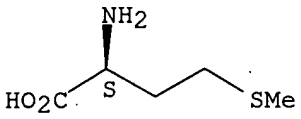


IT **63-68-3**, L-**Methionine**, biological studies
98-92-0, Nicotinamide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**nicotinamide** and **methionine** reduce **liver toxicity** of **methotrexate**)

RN 63-68-3 CAPLUS

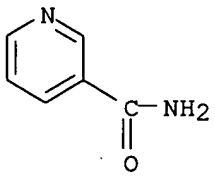
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 98-92-0 CAPLUS

CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:24414 CAPLUS
DOCUMENT NUMBER: 126:126789
TITLE: Protection from **acetaminophen**-induced

liver damage by the synergistic action of low doses of the poly(ADP-ribose) polymerase-inhibitor **nicotinamide** and the antioxidant N-acetylcysteine or the amino acid L-**methionine**

AUTHOR(S): Kroeger, H.; Dietrich, A.; Ohde, M.; Lange, R.; Ehrlich, W.; Kurpisz, M.

CORPORATE SOURCE: DEUTSCHES RHEUMAFORSCHUNGSZENTRUM BERLIN, BERLIN, D-10117, Germany

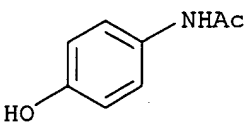
SOURCE: General Pharmacology (1997), 28(2), 257-263
CODEN: GEPHDP; ISSN: 0306-3623

PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An array of therapeutically used analgetic and antirheumatic drugs cause severe **liver damage**. The present study investigates the **hepatoprotective** effects of inhibitors of NAD-dependent adenoribosylation reactions and of antioxidants in analgesic-induced **hepatic** injury. Male NMRI mice were treated PO with 500 mg/kg of **acetaminophen**, and the activities of both glutamate-oxaloacetate transaminase (GOT) and glutamate-pyruvate transaminase (GPT) were determined in serum. The **acetaminophen**-induced release of both GOT and GPT from injured **liver** cells could be inhibited in a dose-dependent manner, when mice were injected addnl. either with increasing amts. (from 25 mg/kg to 100 mg/kg IP) of the poly(ADP-ribose) polymerase (PARP)-inhibitor **nicotinamide**, with increasing amts. (from 25 mg/kg to 100 mg/kg IP) of the antioxidant N-acetylcysteine, or with increasing amts. (from 50 mg/kg to 300 mg/kg IP) of the amino acid L-**methionine**. A combination of both **nicotinamide** and N-acetylcysteine (at the low dose of 12.5 mg/kg IP each) results in a complete protection from **acetaminophen**-induced release of GOT and GPT from injured **liver** cells. A combination of both L-**methionine** and N-acetylcysteine or **nicotinamide** (at the low dose of 12.5 mg/kg IP each) resulted also in complete protection from **acetaminophen**-induced release of GOT and GPT.

IT **103-90-2, Acetaminophen**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(protection from **acetaminophen**-induced **liver damage** by synergistic action of low doses of poly(ADP-ribose) polymerase-inhibitor **nicotinamide** and antioxidant N-acetylcysteine or amino acid L-**methionine**)

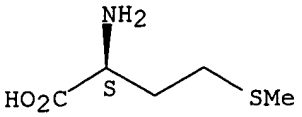
RN 103-90-2 CAPLUS
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



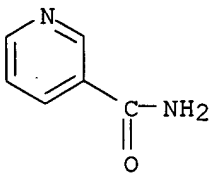
IT **63-68-3**, L-**Methionine**, biological studies
98-92-0, Nicotinamide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protection from **acetaminophen**-induced **liver damage** by synergistic action of low doses of poly(ADP-ribose) polymerase-inhibitor **nicotinamide** and antioxidant N-acetylcysteine or amino acid L-**methionine**)

RN 63-68-3 CAPLUS
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 98-92-0 CAPLUS
CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1075402 CAPLUS
DOCUMENT NUMBER: 143:353368
TITLE: Compositions with reduced **hepatotoxicity**
INVENTOR(S): Bernstein, Joel E.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 4 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005220862	A1	20051006	US 2004-813760	20040331
WO 2005097120	A1	20051020	WO 2005-US9795	20050323

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-813760 A 20040331

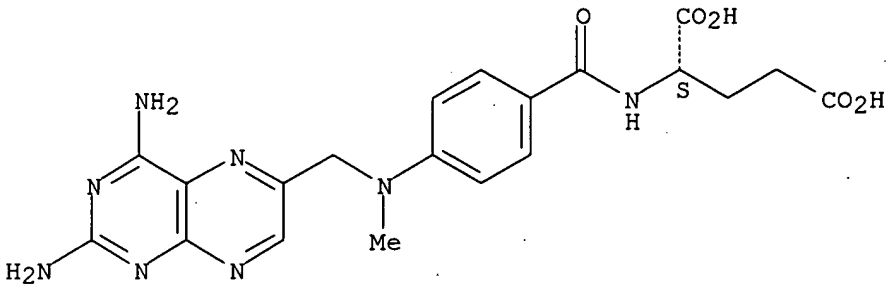
AB Pharmaceutical compns. of **hepatotoxic** compds. are provided in which the **hepatotoxicity** of the compds. is mitigated by including quantities of **nicotinamide** and **methionine** in the composition Folic acid also can be included to further mitigate the **hepatotoxic** effects. The **hepatotoxic** compds. can include **acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole**, divalproex sodium, and **valproic acid**.

IT **59-05-2, Methotrexate 59-67-6, Niacin**
, biological studies **99-66-1, Valproic acid**

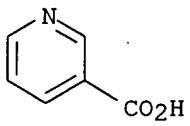
103-90-2, Acetaminophen 76584-70-8, Divalproex sodium **79902-63-9, Simvastatin 86386-73-4, Fluconazole 134523-00-5, Atorvastatin**
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. with reduced **hepatotoxicity**)

RN 59-05-2 CAPLUS
CN L-Glutamic acid, N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]- (9CI) (CA INDEX NAME)

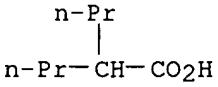
Absolute stereochemistry.



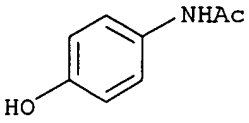
RN 59-67-6 CAPLUS
CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



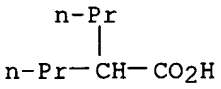
RN 99-66-1 CAPLUS
CN Pentanoic acid, 2-propyl- (9CI) (CA INDEX NAME)



RN 103-90-2 CAPLUS
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



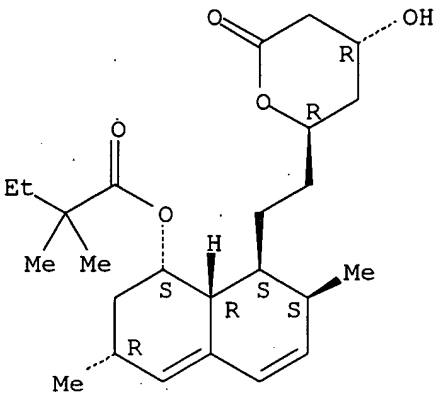
RN 76584-70-8 CAPLUS
CN Pentanoic acid, 2-propyl-, sodium salt (2:1) (9CI) (CA INDEX NAME)



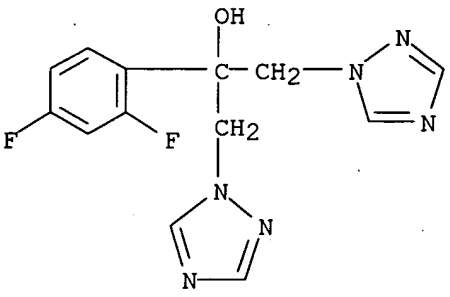
●1/2 Na

RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

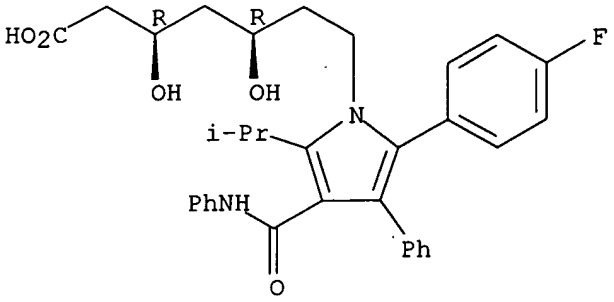


RN 86386-73-4 CAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



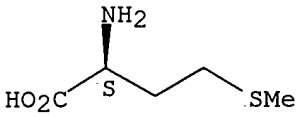
RN 134523-00-5 CAPLUS
CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, (βR,δR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

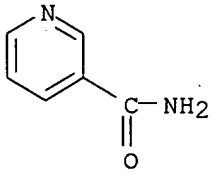


IT **63-68-3, Methionine,** biological studies **98-92-0**
, Nicotinamide
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. with reduced **hepatotoxicity**)
RN 63-68-3 CAPLUS
CN L-Methionine (9CI) (CA INDEX NAME)

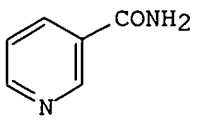
Absolute stereochemistry.



RN 98-92-0 CAPLUS
CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)



L41 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1980:420038 CAPLUS
DOCUMENT NUMBER: 93:20038
TITLE: Long-term perturbation of pyridine nucleotides in rat **liver**
AUTHOR(S): Sturm, Gerlinde; Staerk, Doris; Spengler, Ulrike; Nittinger, Juergen; Jaus, Heinrich H.; Graessle, Barbel; Siebert, Guenther; Romen, Werner
CORPORATE SOURCE: Inst. Biol. Chem. Ernaehrungswiss., Univ. Hohenheim, Fed. Rep. Ger.
SOURCE: Hoppe-Seyler's Zeitschrift fuer Physiologische Chemie (1980), 361(4), 551-8
CODEN: HSZPAZ; ISSN: 0018-4888
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



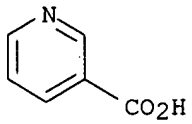
I

AB During a treatment of rats with 4 mmol of **nicotinamide** (I) [**98-92-0**]/kg daily at 12-h intervals for several weeks a permanent rise of **liver** NAD [53-84-9] by several hundred percent is effected; NADP [53-59-8] + NADPH [53-57-6] also increase slightly. Male and female animals of the SIV-50 strain differ in normal and in elevated NAD values; female rats react more markedly and present more pronounced alterations of the **liver**. Besides **nicotinamide**, large amts. of N1-methylnicotinamide [3106-60-3] and nicotinuric acid [583-08-4] and also small amts. of **nicotinamide** N-oxide [1986-81-8] are excreted into the urine. Nicotinuric acid, an unexpected metabolite, was crystallized from urine and identified unequivocally. A permanent load of rats with 1 g **nicotinamide**/kg daily leads to alterations of the **liver** which manifest themselves macroscopically, by **hepatocyte** enlargement, glycogen [9005-79-2] deposits, enzyme decreases, and eventually fatty degeneration. When extra L-**methionine** [**63-68-3**] and glycine [56-40-6] are given in the diet, **liver** alterations are much less severe. It is concluded that the treatment with **nicotinamide** causes a severe amino acid imbalance. During the treatment, animals show symptoms of catatonic stupor, which is discussed in connection with proposals of a **nicotinamide** megatherapy against schizophrenia. On the whole, the exptl. system of permanently elevated NAD concns. is combined with rather serious disadvantages; it is not regarded as a very good general model in studies of **liver** NAD.

IT **59-67-6**, biological studies
RL: BIOL (Biological study)
(as **nicotinamide** metabolite, **nicotinamide** effects of **liver** pyridine nucleotides in relation to)

RN 59-67-6 CAPLUS

CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)

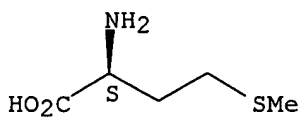


IT **63-68-3**, biological studies
RL: BIOL (Biological study)
(**nicotinamide** induction of **liver toxicity** reversal by glycine and)

RN 63-68-3 CAPLUS

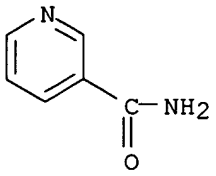
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **98-92-0**
RL: PRP (Properties)
(pyridine nucleotides of **liver** response to, **liver**

toxicity in relation to)
RN 98-92-0 CAPLUS
CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)



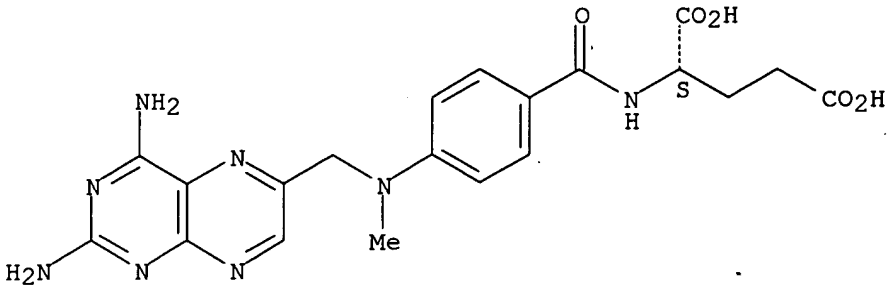
L41 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1154777 CAPLUS
DOCUMENT NUMBER: 143:433974
TITLE: Gene expression profiling and markers for use in the assessment of **hepatotoxicity**
INVENTOR(S): Porter, Mark; Higgs, Brandon; Mendrick, Donna; Elashoff, Michael
PATENT ASSIGNEE(S): Gene Logic, Inc., USA
SOURCE: PCT Int. Appl., 264 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005100989	A2	20051027	WO 2005-US11532	20050407

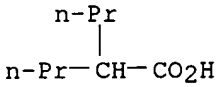
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-559949P P 20040407
AB Methods of using the effects of a substance on gene expression profiles are described for use in assessing their **toxicity**, especially **hepatotoxicity**, are described. The invention also includes microarrays, computer systems comprising the **toxicity** prediction models, as well as methods of using the computer systems by remote users for determining the **toxicity** of test agents. A database of gene expression profiles for rat **liver** using a broad range of drugs, com. chems., and known poisons is developed.
IT **59-05-2 99-66-1 103-90-2 79902-63-9, Simvastatin**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(assessing **hepatotoxicity** of; gene expression profiling and markers for use in assessment of **hepatotoxicity**)
RN 59-05-2 CAPLUS
CN L-Glutamic acid, N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]- (9CI) (CA INDEX NAME)

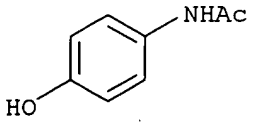
Absolute stereochemistry.



RN 99-66-1 CAPLUS
CN Pentanoic acid, 2-propyl- (9CI) (CA INDEX NAME)

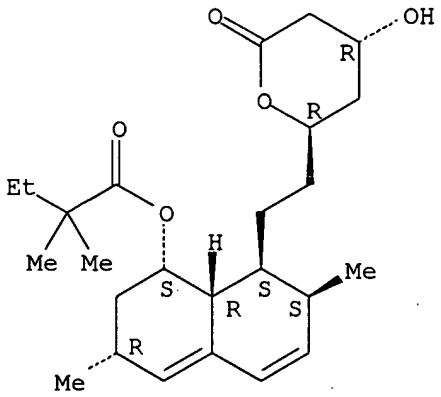


RN 103-90-2 CAPLUS
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



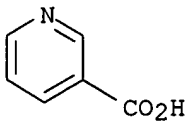
L41 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:47659 CAPLUS
DOCUMENT NUMBER: 124:169433
TITLE: Methylene blue plus light-induced lipid peroxidation in rat **liver** microsomes: inhibition by **nicotinamide** (vitamin B3) and other

antioxidants
AUTHOR(S): Kamat, Jayashree P.; Devasagayam, Thomas P. A.
CORPORATE SOURCE: Bombay-400, India
SOURCE: Chemico-Biological Interactions (1996), 99(1-3), 1-16
CODEN: CBINA8; ISSN: 0009-2797
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Methylene blue plus visible light, in the presence of oxygen, induced lipid peroxidn. in rat **liver** microsomes, as assessed by the formation of thiobarbituric acid reactive substances (TBARS), lipid hydroperoxides and the loss of membrane-bound enzymes. Peroxidn. was enhanced by deuteration of the buffer and inhibited by scavengers of singlet oxygen (1O2) and superoxide (O2-). The **damage** induced seemed to be mainly due to Type II involving 1O2 and to a lesser extent Type I reactions with O2- and hydroxyl radical (OH) as intermediates. **Nicotinamide** or vitamin B3, an endogenous metabolite occurring at high concns. in tissues, had a relatively high rate constant of 1.8 + 108 M-1 s-1 with 1O2 and had a significant inhibitory effect on lipid peroxidn. induced by photosensitization. This effect was both time- and concentration-dependent, high inhibition being associated with millimolar concns.

Chemical related endogenous compds. like tryptophan and isonicotinic acid also had significant inhibitory properties. Similar protective effects were observed with natural antioxidants such as β-carotene, canthaxanthin, lipoic acid, glutathione, α-tocopherol and to a lesser extent ascorbic acid. **Nicotinamide** was a more effective antioxidant than ascorbic acid. It also showed a similar inhibitory effect against NADPH-ADP-Fe3+-induced lipid peroxidn. Our results suggest that **nicotinamide** had significant ability to protect against photosensitization-induced cytotoxicity and cell **damage** and that it may do so by its ability to react with 1O2 and other reactive oxygen species.

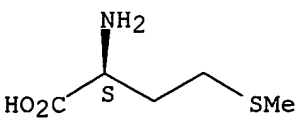
IT **59-67-6**, 3-Pyridinecarboxylic acid, biological studies
63-68-3, **Methionine**, biological studies **98-92-0**
, **Nicotinamide**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methylene blue plus light-induced lipid peroxidn. in rat **liver** microsomes: **nicotinamide** (vitamin B3) and other antioxidants)

RN 59-67-6 CAPLUS
CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



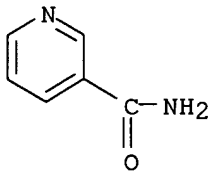
RN 63-68-3 CAPLUS
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 98-92-0 CAPLUS

CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)

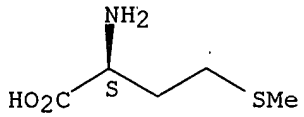


L41 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1959:101245 CAPLUS
DOCUMENT NUMBER: 53:101245
ORIGINAL REFERENCE NO.: 53:18278h-i,18279a
TITLE: The need of combining **methionine** with nicotinic acid and **nicotinamide** when administering these pyridine compounds in very high doses
AUTHOR(S): Cedrangolo, F.; Scala, E.
CORPORATE SOURCE: Univ. Naples
SOURCE: Minerva Medica (1959) 1299
CODEN: MIMEAO; ISSN: 0026-4806
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

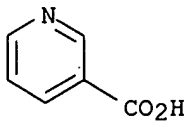
AB Since both nicotinic acid and **nicotinamide** (I) are eliminated as N-methyl-2-pyridonecarboxamide, high doses lead to rapid depletion of Me group reserve, with serious results such as fatty degeneration of the **liver**. In rats, 0.5 g. of I/100 g. of diet causes considerable fatty degeneration in the **liver**, together with renal hemorrhage (Foa, et al., C.A. 39, 4654). In normal humans, 400 mg./day has shown signs of **hepatic** insufficiency as a pos. Wallace-Diamond test (Scala and Janella, C.A. 51, 9940i). This has now been confirmed in numerous patients. Doses of I over 100 mg. should be combined with suitable amts. of **methionine**.

IT **63-68-3, Methionine**
(in **nicotinamide** and nicotinic acid treatment)
RN 63-68-3 CAPLUS
CN L-Methionine (9CI) (CA INDEX NAME)

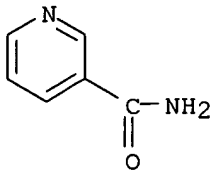
Absolute stereochemistry.



IT **59-67-6**, Nicotinic acid **98-92-0, Nicotinamide**
(**toxicity** of, **methionine** prevention of)
RN 59-67-6 CAPLUS
CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



RN 98-92-0 CAPLUS
CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)

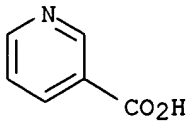


L41 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:443026 CAPLUS
DOCUMENT NUMBER: 144:102210
TITLE: Profiles of Metabolites and Gene Expression in Rats with Chemically Induced **Hepatic** Necrosis
AUTHOR(S): Heijne, Wilbert; Lamers, Robert-Jan; Van Bladeren, Peter; Groten, John; Van Nesselrooij, Joop; Van Ommen, Ben
CORPORATE SOURCE: TNO Nutrition and Food Research, Zeist, Neth.
SOURCE: Toxicologic Pathology (2005), 33(4), 425-433
CODEN: TOPADD; ISSN: 0192-6233
PUBLISHER: Taylor & Francis, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study investigated whether integrated anal. of transcriptomics and metabolomics data increased the sensitivity of detection and provided new insight in the mechanisms of **hepatotoxicity**. Metabolite levels in plasma or urine were analyzed in relation to changes in **hepatic** gene expression in rats that received bromobenzene to induce acute **hepatic** centrilobular necrosis. Bromobenzene-induced lesions were only observed after treatment with the highest of 3 dose levels. Multivariate statistical anal. showed that metabolite profiles of blood plasma were largely different from controls when the rats were treated with bromobenzene, also at doses that did not elicit histopathol. changes. Changes in levels of genes and metabolites were related to the degree of necrosis, providing putative novel markers of **hepatotoxicity**. Levels of endogenous metabolites like alanine, lactate, tyrosine and dimethylglycine differed in plasma from treated and control rats. The metabolite profiles of urine were found to be reflective of the exposure levels. This integrated anal. of **hepatic** transcriptomics and plasma metabolomics was able to more sensitively detect changes related to **hepatotoxicity** and discover novel markers. The relation between gene expression and metabolite levels was explored and addnl. insight in the role of various biol. pathways in bromobenzene-induced **hepatic** necrosis was obtained, including the involvement of apoptosis and changes in glycolysis and amino acid metabolism

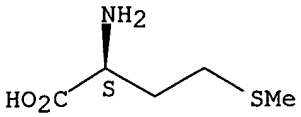
IT **59-67-6**, 3-Pyridinecarboxylic acid, biological studies
63-68-3, L-**Methionine**, biological studies
98-92-0, **Nicotinamide**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(profiles of metabolites and gene expression in rats with chemical induced **hepatic** necrosis)

RN 59-67-6 CAPLUS
CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)

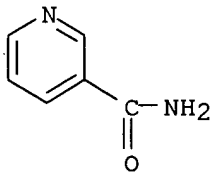


RN 63-68-3 CAPLUS
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 98-92-0 CAPLUS
CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)



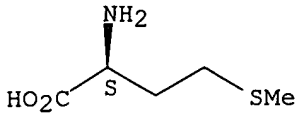
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1958:41446 CAPLUS
DOCUMENT NUMBER: 52:41446
ORIGINAL REFERENCE NO.: 52:7475c-f
TITLE: Role of **methionine** in the metabolism of tryptophan by rats treated with carbon tetrachloride
AUTHOR(S): Banerjee, Sachchidananda; Chattopadhyay, Dhurjatiprasad
CORPORATE SOURCE: Presidency Coll., Calcutta
SOURCE: Indian Journal of Medical Research (1913-1988) (1957), 45, 531-5
CODEN: IJMRAQ; ISSN: 0019-5340
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

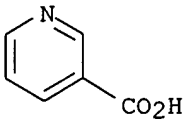
AB The injection of CCl4 caused a decrease in urinary excretions of nicotinic acid (I), quinolinic acid (II), N1-methyl **nicotinamide** (III) and creatinine (IV). It possibly indicated that the **liver** had been damaged and could not synthesize I efficiently from tryptophan. When the rats were injected with **methionine**, although there was no change in the urinary secretion of I and II, a significant increase in the urinary excretion of III and IV was noted indicating that the labile CH3 group of **methionine** helps the methylating mechanism. When CCl4 was injected along with the injection of **methionine**, no decrease in the urinary excretions of, I, II, III, or IV was observed. It therefore seems that **methionine** somehow protects the animal from CCl4 poisoning. Total fat, free cholesterol and esterified cholesterol contents of **livers** of CCl4 injected rats were higher than the corresponding values in normal rats. Simultaneous injection of **methionine** prevented the accumulation of increased amts. of lipides in the **liver**. CCl4 poisoning did not affect the intestine indicating that the **liver** is the principal site of synthesis of I from tryptophan in rats.

IT **63-68-3, Methionine**
(effect on tryptophan metabolism in **liver damage**)
RN 63-68-3 CAPLUS
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **59-67-6**, Nicotinic acid
(in urine, in **liver** disorder, **methionine** effect on)
RN 59-67-6 CAPLUS
CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



L41 ANSWER 10 OF 20 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005348235 EMBASE
TITLE: Protection from **acetaminophen**-induced **liver damage** by the synergistic action of low doses of the poly(ADP-ribose) polymerase-inhibitor **nicotinamide** and the antioxidant N-acetylcysteine or the amino acid L-**methionine**.
AUTHOR: Kroger H.; Dietrich A.; Ohde M.; Lange R.; Ehrlich W.; Kurpisz M.
CORPORATE SOURCE: H. Kroger, Deutsches Rheumaforschungszentrum Berlin, Monbijoustr. 2, D-10117 Berlin, Germany
SOURCE: Vascular Pharmacology, (1997) Vol. 28, No. 2, pp. 257-263.
Refs: 32
ISSN: 1537-1891 CODEN: VPAHAJ
PUBLISHER IDENT.: S 0306-3623(96)00181-4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 1 Sep 2005
Last Updated on STN: 1 Sep 2005

AB An array of therapeutically used analgetic and antirheumatic drugs cause severe **liver damage**. The present study investigates the **hepatoprotective** effects of inhibitors of NAD-dependent adenoribosylation reactions and of antioxidants in analgesic-induced **hepatic** injury. Male NMRI mice were treated PO with 500 mg/kg of **acetaminophen**, and the activities of both glutamate-oxaloacetate transaminase (GOT) and glutamate-pyruvate transaminase (GPT) were determined in serum. The **acetaminophen**-induced release of both GOT and GPT from injured **liver** cells could be inhibited in a dose-dependent manner, when mice were injected additionally either with increasing amounts (from (25 mg/kg to 100 mg/kg IP) of the PARP-inhibitor **nicotinamide**, with increasing amounts (from 25 mg/kg to 100 mg/kg IP) of the antioxidant N-acetylcysteine, or with increasing amounts (from 50 mg/kg to 300 mg/kg IP) of the amino acid L-**methionine**. A combination of both **nicotinamide** and N-acetylcysteine (at the low dose of 12.5 mg/kg IP each) results in a complete protection from

acetaminophen-induced release of GOT and GPT from injured **liver** cells. A combination of both L-**methionine** and N-acetylcysteine or **nicotinamide** (at the low dose of 12.5 mg/kg IP each) resulted also in complete protection from **acetaminophen** -induced release of GOT and GPT. Copyright .COPYRGT. 1997 Elsevier Science Inc.

L41 ANSWER 11 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2002462179 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12221238
TITLE: Acute valproate administration impairs **methionine** metabolism in rats.
AUTHOR: Ubeda Natalia; Alonso-Aperte Elena; Varela-Moreiras Gregorio
CORPORATE SOURCE: Seccion de Nutricion, Bromatologia y Dietetica, Facultad de Ciencias Experimentales y de la Salud, Universidad San Pablo CEU, Madrid, Spain.. nubeda@ceu.es
SOURCE: The Journal of nutrition, (2002 Sep) Vol. 132, No. 9, pp. 2737-42.
Journal code: 0404243. ISSN: 0022-3166.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 11 Sep 2002
Last Updated on STN: 7 Feb 2003
Entered Medline: 6 Feb 2003

AB Valproate (VPA) is a drug widely used to treat epilepsy, but it has serious adverse effects including **hepatotoxicity**, teratogenicity and antifolate activity. The mechanism underlying VPA **toxicity** is unclear although an interaction with folate and other metabolites involved in **methionine** metabolism has been suggested. The present study was undertaken to evaluate potential changes in the metabolic function of the **methionine** cycle after acute exposure to a single dose of valproate. Female Wistar rats (n = 30) were treated with 400 mg/kg of VPA. Different groups of six rats were killed at 1 (t1), 3 (t3), 6 (t6), 9 (t9), and 24 (t24) hours after the injection. One group of rats was untreated (n = 6) and was considered the control group. The most pronounced effects of VPA administration were observed 1 h after drug injection. VPA induced a 56% reduction in **methionine** adenosyltransferase activity and a 54% reduction in plasma **vitamin B**-6. Increases in the **hepatic** concentration of S-adenosylhomocysteine and oxidized glutathione, and a reduction in the S-adenosylmethionine/S-adenosylhomocysteine transmethylation ratio also occurred at 1 h. All of these alterations, however, were normalized within 24 h, parallel with a decrease in serum VPA concentration. The acute effects of VPA suggest that the alterations in the **methionine** cycle could be the common mechanism underlying the **hepatotoxic**, teratogenic and antifolate effects of the drug.

L41 ANSWER 12 OF 20 EMBASE
ACCESSION NUMBER: 97048562 EMBASE
DOCUMENT NUMBER: 1997048562
TITLE: Male rats fed methyl- and folate-deficient diets with or without **niacin** develop **hepatic** carcinomas associated with decreased tissue NAD concentrations and altered poly(ADP-ribose) polymerase activity.
AUTHOR: Henning S.M.; Swendseid M.E.; Coulson W.F.
CORPORATE SOURCE: S.M. Henning, Community Health Sciences, School of Public Health, University of California, Los Angeles, CA 90095,

United States
SOURCE: Journal of Nutrition, (1997) Vol. 127, No. 1, pp. 30-36. .
Refs: 26
ISSN: 0022-3166 CODEN: JONUAI
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 10 Mar 1997
Last Updated on STN: 10 Mar 1997

AB Folate is an essential cofactor in the generation of endogenous **methionine**, and there is evidence that folate deficiency exacerbates the effects of a diet low in choline and **methionine**, including alterations in poly(ADP-ribose) polymerase (PARP) activity, an enzyme associated with DNA replication and repair. Because PARP requires NAD as its substrate, we postulated that a deficiency of both folate and **niacin** would enhance the development of **liver** cancer in rats fed a diet deficient in **methionine** and choline. In two experiments, rats were fed choline- and folate-deficient, low **methionine** diets containing either 12 or 8% casein (12% MCFD, 8% MCFD) or 6% casein and 6% gelatin with **niacin** (MCFD) or without **niacin** (MCFND) and were compared with folate-supplemented controls. **Liver** NAD concentrations were lower in all methyl-deficient rats after 2-17 mo. At 17 mo, NAD concentrations in other tissues of rats fed these diets were also lower than in controls. Compared with control values, **liver** PARP activity was enhanced in rats fed the 12% MCFD diet but was lower in MCFND-fed rats following a further reduction in **liver** NAD concentration. These changes in PARP activity associated with lower NAD concentrations may slow DNA repair and enhance DNA **damage**. Only rats fed the MCFD and MCFND diets developed **hepatocarcinomas** after 12-17 mo. In Experiment 2, **hepatocarcinomas** were found in 100% of rats fed the MCFD and MCFND diets. These preliminary results indicate that folic acid deficiency enhances tumor development. Because tumors developed in 100% of the MCFD-fed rats and because tissue concentrations of NAD in these animals were also low, further studies are needed to clearly define the role of **niacin** in methyldeficient rats.

L41 ANSWER 13 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2002162732 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11895163
TITLE: **Niacin** (nicotinic acid) in non-physiological doses causes hyperhomocysteineaemia in Sprague-Dawley rats.
AUTHOR: Basu Tapan K; Makhani Neelam; Sedgwick Gary
CORPORATE SOURCE: Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Canada.. tbasu@afns.ualberta.ca
SOURCE: The British journal of nutrition, (2002 Feb) Vol. 87, No. 2, pp. 115-9.
Journal code: 0372547. ISSN: 0007-1145.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 17 Mar 2002
Last Updated on STN: 23 Apr 2002
Entered Medline: 22 Apr 2002

AB **Niacin** (nicotinic acid) in its non-physiological dose level is known to be an effective lipid-lowering agent; its potential risk as a

therapeutic agent, however, has not been critically considered. Since **niacin** is excreted predominantly as methylated pyridones, requiring **methionine** as a methyl donor, the present study was undertaken to examine whether metabolism of the amino acid is altered in the presence of large doses of **niacin**. Male Sprague-Dawley rats were given a nutritionally adequate, semi-synthetic diet containing **niacin** at a level of either 400 or 1000mg/kg diet (compared to 30mg/kg in the control diet) for up to 3 months. Supplementation with **niacin** (1,000 mg/kg diet) for 3 months resulted in a significant increase in plasma and urinary total homocysteine levels; this increase was further accentuated in the presence of a high **methionine** diet. The hyperhomocysteineaemia was accompanied by a significant decrease in plasma concentrations of vitamins B6 and B12, which are cofactors for the metabolism of homocysteine. The homocysteine-raising action of **niacin**, in particular, has an important toxicological implication, as hyperhomocysteineaemia is considered to be an independent risk factor for arterial occlusive disease. The **niacin** -associated change in homocysteine status may be an important limiting factor in the use of this vitamin as a lipid-lowering agent.

L41 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:162309 CAPLUS
DOCUMENT NUMBER: 140:205217
TITLE: System for exsanguinous metabolic support of an organ or tissue
INVENTOR(S): Brasile, Lauren
PATENT ASSIGNEE(S): Breonics, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 25 pp., Cont.-in-part of U.S. Ser. No. 849,618.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004038192	A1	20040226	US 2003-443452	20030522
US 6642045	B1	20031104	US 2000-547843	20000412
US 2002012988	A1	20020131	US 2001-849618	20010504
US 6582953	B2	20030624		
US 2004038193	A1	20040226	US 2003-650986	20030827
WO 2004105484	A1	20041209	WO 2004-US16085	20040521

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

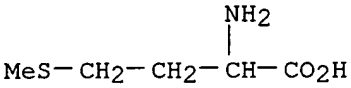
PRIORITY APPLN. INFO.:		
US 1999-129257P	P	19990414
US 2000-547843	A2	20000412
US 2001-849618	A2	20010504
WO 2000-US9894	W	20000413
US 2003-443452	A	20030522

AB An exsanguinous metabolic support system for maintaining an organ or tissue at a near normal metabolic rate is disclosed that employs a warm perfusion solution capable of altering the production of nitric oxide (NO) in an

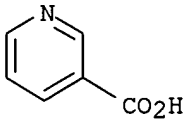
organ or tissue and supporting the metabolism of the organ or tissue at normothermic temps. Perfusion with the solution of the invention can therefore be used to regulate nitric oxide production in situations where it is desirable to do so, e.g. to prevent reperfusion injury. The system also monitors parameters of the circulating perfusion solution, such as pH, temperature, osmolarity, flow rate, vascular pressure and partial pressure of respiratory gases, and nitric oxide (NO) concentration and regulates them to insure that the organ is maintained under near-physiol. conditions. Use of the system for long-term maintenance of organs for transplantation, for resuscitation and repair of organs having sustained warm ischemic **damage**, to treat cardiovascular disorders, to prevent reperfusion injury, as a pharmaceutical delivery system and prognosticator of post-transplantation organ function is also disclosed.

IT **59-51-8, Methionine 59-67-6,** Nicotinic Acid, biological studies **98-92-0, Niacinamide**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(system for exsanguinous metabolic support of an organ or tissue)

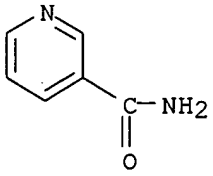
RN 59-51-8 CAPLUS
CN Methionine (9CI) (CA INDEX NAME)



RN 59-67-6 CAPLUS
CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



RN 98-92-0 CAPLUS
CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)



L41 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

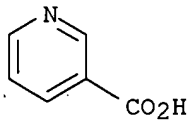
ACCESSION NUMBER:	1953:32699 CAPLUS
DOCUMENT NUMBER:	47:32699
ORIGINAL REFERENCE NO.:	47:5557i,5558a-d
TITLE:	Pharmacological studies on isonicotinic acid hydrazide
AUTHOR(S):	Garattini, S.; Grassi, C.; Mantegazza, P.; Morvillo, V.; Tommasini, R.; Trabucchi, E.
CORPORATE SOURCE:	Univ. Milan
SOURCE:	Atti della Societa Lombarda di Scienze Mediche e Biologiche (1952), 7(No. Spec.), 1-19;English summary 18-19 CODEN: ASLBAG; ISSN: 0365-690X
DOCUMENT TYPE:	Journal
LANGUAGE:	Unavailable

AB Isonicotinic acid hydrazide (I) showed a more intense inhibiting action than streptomycin on Koch's bacilli in vitro. Vitamins B1, B2, and B6, p-aminobenzoic acid, uracil, thymine, **nicotinamide**, choline, **methionine**, folic acid, pantothenic acid, isonicotinic acid, and isonicotinamide were inefficient in counteracting I action. (1) p-Aminobenzoic acid hydrazide, nicotinic acid hydrazide, and isonicotinic acid amide, (2) succinic acid bishydrazide, and (3) pyrazincarboxylic acid hydrazide had, resp., (1) no, (2) some, and (3) a considerable inhibiting action on Koch's bacilli. Also in vivo, in rats, the effect of I was higher than that of streptomycin. Intravenously injected I was distributed rapidly to the various tissues, especially to **liver**; exchanges through the blood-tissue barrier occurred in both senses; I urinary excretion occurred within some hrs. after injection. I was rapidly destroyed in the organism (removal of both the terminal N, with formation of NH3 and isonicotinamide, and of the whole hydrazine group with formation of isonicotinic acid). Also in vitro I was decomposed (lateral chain taken off) by slices of **liver**, lung, and brain and by yeasts; this action was inhibited by thiourea and p-aminobenzoic acid. Metabolisms of I and of isonicotinic acid and its amide were different from that of **nicotinamide** since the pyridine N was not alkylated. The nervous phenomena due to I administration to animals were also investigated: the association of thiourea and p-aminobenzoic acid with I attenuated its convulsive effect, the association of pyruvic acid enhanced the resistance of animals to the **toxic** effects of I. The administration of I lowered the pyruvic acid level of blood in humans and animals (and of the brain of the latter), and in sound subjects caused also a drop of blood eosinophils and in guinea pigs a considerable drop of the ascorbic acid content of adrenal glands (by high I doses).

IT **59-67-6**, Nicotinic acid
(hydrazides, bacteriostatic action on tubercle bacilli)

RN 59-67-6 CAPLUS

CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



L41 ANSWER 16 OF 20 EMBASE

ACCESSION NUMBER: 2001398967 EMBASE

TITLE: Folic acid revisited.

AUTHOR: Hazra A.; Kumar Tripathi S.

CORPORATE SOURCE: A. Hazra, 17/2/4B Chakraberia Road (South), Calcutta 700025, India. blowfans@cal2.vsnl.net.in

SOURCE: Indian Journal of Pharmacology, (2001) Vol. 33, No. 5, pp. 322-342. .
Refs: 114
ISSN: 0253-7613 CODEN: INJPD2

COUNTRY: India

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index
025 Hematology
020 Gerontology and Geriatrics
021 Developmental Biology and Teratology
036 Health Policy, Economics and Management
005 General Pathology and Pathological Anatomy

038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Nov 2001
Last Updated on STN: 30 Nov 2001

AB Folic acid, or pteroylglutamic acid, is a well-known water soluble vitamin of the B-complex group. It is necessary for DNA synthesis and normal erythropoiesis. Tetrahydrofolate, the active form of this vitamin, functions as a conenzyme in various metabolic reactions involving transfer of one-carbon moieties. Folate and **vitamin B**(12) metabolic pathways intersect at the conversion of homocysteine to **methionine**. Human beings cannot synthesize this vitamin and must obtain performed folate through dietary sources like green leafy vegetables, cereals, fruits, organ meats and yeast. Synthetic folic acid is more bioavailable than food folate. Absorption is predominantly from the upper small intestine and elimination predominantly renal, with modest **hepatic** storage. The daily requirement varies by age and is greater during pregnancy and lactation. Apart from increased demand, folate deficiency can occur in malnutrition, malabsorption, chronic hemolytic anemias, chronic alcoholism, repeated hemodialysis, and unusual dietary situations like total parenteral nutrition. The use of certain antiepileptic, antimalarial, antimicrobial and anticancer drugs may interfere with the absorption, conversion or utilization of folate leading to megaloblastic anemia. The primary therapeutic indication is in the prophylaxis and treatment of deficiency states. Pharmacological supplementation is recommended in situations like pregnancy (for preventing macrocytic anemia, occurrence or recurrence of neural tube defects, counteracting teratogenic effect of anticonvulsants, etc.), malnutrition, malabsorption and chronic hemodialysis. It may be supplemented during lactation, in infants, the elderly, alcoholics, and in renal failure patients. Folic acid may also reduce orofacial clefting and ameliorate **methotrexate toxicity** in rheumatoid arthritis. Pharmacological dose are well-tolerated but folate supplementation aloen in megaloblastic anemia primarily due to **vitamin B**(12) deficiency can worsen the neurological condition. Of late, interest in folic acid has grown with the realization that modest folate supplementation can prevent hyperhomocysteinemia, which is an independent graded risk factor for atherosclerotic cardiovascular disease, and is possibly beneficial in certain cancers. The recent stipulation for mandatory folate fortification of cereal products in USA and the inclusion of folic acid in the WHO model list of essential drugs recognize the increasing importance of folate in human nutrition. Indeed, folic acid has revisited with new therapeutic applications and its mysteries are still unfolding more than 7 decades after its discovery.

L41 ANSWER 17 OF 20 EMBASE
ACCESSION NUMBER: 2002185488 EMBASE
TITLE: S-adenosyl-L-**methionine** (SAMe) for the treatment of **acetaminophen toxicity** in a dog.
AUTHOR: Wallace K.P.; Center S.A.; Hickford F.H.; Warner K.L.; Smith S.
CORPORATE SOURCE: K.P. Wallace, Department of Clinical Sciences, New York State Coll. Veterinary Med., Cornell University, P.O. Box 25, Ithaca, NY 14853-6401, United States
SOURCE: Journal of the American Animal Hospital Association, (2002) Vol. 38, No. 3, pp. 246-254. .
Refs: 53
ISSN: 0587-2871 CODEN: JAAHBL
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 025 Hematology
030 Pharmacology

037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 6 Jun 2002
Last Updated on STN: 6 Jun 2002

AB An 8-month-old, spayed female Shetland sheepdog presented 48 hours after ingesting **acetaminophen** (1 gm/kg body weight). On presentation, the dog was laterally recumbent and hypovolemic. The dog had brown mucous membranes, severe Heinz-body hemolytic anemia, bleeding tendencies, and a red blood cell (RBC) glutathione (GSH) concentration that was 10% of reference values, despite a regenerative erythroid response. Treatment with s-adenosyl-l-**methionine** (SAMe) as a GSH donor successfully rescued this dog, despite the animal's late presentation after drug ingestion. A loading dose (40 mg/kg body weight) of a stable SAMe salt per os was followed by a maintenance dose (20 mg/kg body weight) sid for 7 days. Additional therapeutic interventions included an intravenous (IV) infusion of one unit of packed RBCs (on admission), IV fluid support (3 days), and famotidine (7 days) to reduce gastric acidity. Sequential assessment of RBC GSH concentrations and RBC morphology documented response to antidote administration within 72 hours. This case suggests that SAMe may provide a therapeutic option for treatment of **acetaminophen** toxicosis in dogs capable of retaining an orally administered antidote and maintaining adequate **hepatic** function for metabolism of SAMe to its thiol substrates.

L41 ANSWER 18 OF 20 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005118231 EMBASE
TITLE: Inhibition of CYP2E1 catalytic activity in vitro by S-adenosyl-L-**methionine**.
AUTHOR: Caro A.A.; Cederbaum A.I.
CORPORATE SOURCE: A.A. Caro, Dept. of Pharmacol. and Biol. Chem., Mount Sinai School of Medicine, New York, NY 10029, United States. andres.caro@mssm.edu
SOURCE: Biochemical Pharmacology, (1 Apr 2005) Vol. 69, No. 7, pp. 1081-1093.
Refs: 44
ISSN: 0006-2952 CODEN: BCPCA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 7 Apr 2005
Last Updated on STN: 7 Apr 2005

AB The objective of this work was to evaluate the possible in vitro interactions of S-adenosyl-L-**methionine** (SAM) and its metabolites S-(5'-Adenosyl)-l-homocysteine (SAH), 5'-Deoxy-5'-(methylthio) adenosine (MTA) and **methionine** with cytochrome P450 enzymes, in particular CYP2E1. SAM (but not SAH, MTA or **methionine**) produced a type II binding spectrum with **liver** microsomal cytochrome P450 from rats treated with acetone or isoniazid to induce CYP2E1. Binding was less effective for control microsomes. SAM did not alter the carbon monoxide binding spectrum of P450, nor denature P450 to P420, nor inhibit the activity of NADPH-P450 reductase. However, SAM inhibited the catalytic activity of CYP2E1 with typical substrates such as p-nitrophenol, ethanol, and dimethylnitrosamine, with an IC(50) around 1.5-5 mM. SAM was a non-competitive inhibitor of CYP2E1 catalytic activity and its inhibitory actions could not be mimicked by **methionine**, SAH or MTA. However, SAM did not inhibit the

oxidation of ethanol to α-hydroxyethyl radical, an assay for hydroxyl radical generation. In microsomes engineered to express individual human P450s, SAM produced a type II binding spectrum with CYP2E1-, but not with CYP3A4-expressing microsomes, and SAM was a weaker inhibitor against the metabolism of a specific CYP3A4 substrate than a specific CYP2E1 substrate. SAM also inhibited CYP2E1 catalytic activity in intact HepG2 cells engineered to express CYP2E1. These results suggest that SAM interacts with cytochrome P450s, especially CYP2E1, and inhibits the catalytic activity of CYP2E1 in a reversible and non competitive manner. However, SAM is a weak inhibitor of CYP2E1. Since the K(i) for SAM inhibition of CYP2E1 activity is relatively high, inhibition of CYP2E1 activity is not likely to play a major role in the ability of SAM to protect against the **hepatotoxicity** produced by toxins requiring metabolic activation by CYP2E1 such as **acetaminophen**, ethanol, carbon tetrachloride, thioacetamide and carcinogens.

L41 ANSWER 19 OF 20 EMBASE

ACCESSION NUMBER: 2004257294 EMBASE
TITLE: The effect of fibrates and other lipid-lowering drugs on plasma homocysteine levels.
AUTHOR: Dierkes J.; Westphal S.; Luley C.
CORPORATE SOURCE: Dr. J. Dierkes, Inst. of Clinica Chem./Biochemistry, University Hospital Magdeburg, Leipziger Str. 44, 39120 Magdeburg, Germany. jutta.dierkes@medizin.uni-magdeburg.de
SOURCE: Expert Opinion on Drug Safety, (2004) Vol. 3, No. 2, pp. 101-111. .
Refs: 84
ISSN: 1474-0338 CODEN: EODSA
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 1 Jul 2004
Last Updated on STN: 1 Jul 2004

AB Hyperlipidaemia is a major risk factor for cardiovascular disease. The drugs of choice for the treatment of hyperlipidaemia are either fibrates, in the case of hypertriglyceridaemia, or statins, in the case of hypercholesterolaemia. Recently, it has been shown that some of the most prescribed fibrates cause hyperhomocysteinaemia, which itself has been recognised as a cardiovascular risk factor. In particular, fenofibrate and bezafibrate lead to a 20 - 40% elevation of plasma levels of the atherogenic amino acid homocysteine, thereby possibly counteracting the desired cardiovascular protection. The most likely mechanism for this increase is an alteration of creatine-creatinine metabolism and changes in methyl transfer. Gemfibrozil does not increase homocysteine. Statins have no effect on the plasma homocysteine concentration. The increase of plasma homocysteine after fenofibrate can be lowered by the concurrent administration of folic acid and **vitamins B**(12) and B(6). Thus, patients with hypertriglyceridaemia can either be concurrently treated with fenofibrate and vitamins or with gemfibrozil. 2004

L41 ANSWER 20 OF 20 MEDLINE on STN
ACCESSION NUMBER: 90252753 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2187335
TITLE: Anti-leukemic potential of methyl-cobalamin inactivation by

nitrous oxide.

AUTHOR: Abels J; Kroes A C; Ermens A A; van Kapel J; Schoester M; Spijkers L J; Lindemans J
CORPORATE SOURCE: Institute of Hematology, Erasmus University, Rotterdam, The Netherlands.

SOURCE: American journal of hematology, (1990 Jun) Vol. 34, No. 2, pp. 128-31. Ref: 45
Journal code: 7610369. ISSN: 0361-8609.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199006
ENTRY DATE: Entered STN: 20 Jul 1990
Last Updated on STN: 20 Jul 1990
Entered Medline: 18 Jun 1990

AB Myelo-cytotoxicity of extended nitrous oxide (N2O) inhalation was described almost forty years ago and then incidentally applied already with temporary success for suppressing leukemia. In 1948 the accompanying megaloblastic maturation arrest was explained by inactivation of the methylcobalamin coenzyme and subsequent folate deficiency. We studied the anti-leukemic effect of N2O on a transplantable acute leukemia in B(rown) N(orway) rats. Progression of this B,N,M(yelocytic)L(eukemia) was measured as spleen and **liver** weights, and leukemic blood cell counts. The deoxyuridine (dU)-suppression test provided in vitro indication of the functional folate activity of leukemic cells. Breathing of N2O-oxygen considerably reduced but did not eradicate, BNML-proliferation. Addition of anti-metabolites, interfering with some enzyme in the folate metabolism beyond the methylcobalamin co-enzyme dependent **methionine** synthase step, acted at least synergistically. The anti-leukemic effect of cycloleucine, which reduces S-adenosyl-**methionine** synthesis by inactivation of **methionine** adenosyltransferase, was moderate but became much stronger with N2O inhalation. **Methotrexate**, a potent anti-leukemic agent by inhibiting tetrahydrofolate (THF) generation through inactivation of di-HF reductase, became highly anti-BNML, even in low dosage when combined with or preceded by N2O. 5-Fluorouracil, which inhibits methylene-THF dependent thymidilate synthase, itself was surprisingly anti-BNML, but also became much more potent with previous or concomitant N2O exposure. Preliminary dU-suppression test results with human acute leukemia cells, exposed to N2O and/or folate antagonists in vitro, correlated well with the in vivo BNML-experiments. Combining the anticobalamin activity of N2O with an anti-folate therefore seems to be a promising chemotherapeutic approach.

=>

L42 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1075402 CAPLUS
DOCUMENT NUMBER: 143:353368
TITLE: Compositions with reduced **hepatotoxicity**
INVENTOR(S): Bernstein, Joel E.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 4 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005220862	A1	20051006	US 2004-813760	20040331
WO 2005097120	A1	20051020	WO 2005-US9795	20050323

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

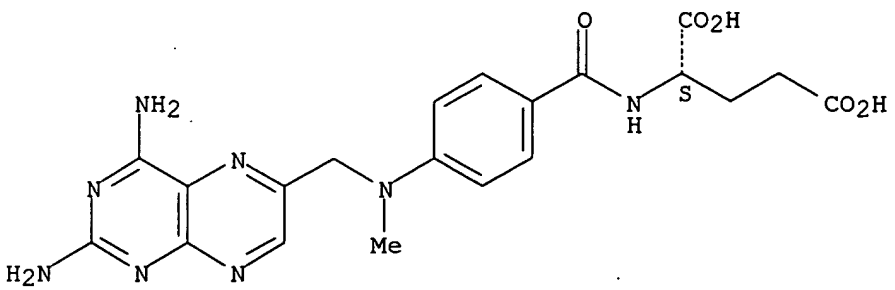
PRIORITY APPLN. INFO.: US 2004-813760 A 20040331

AB Pharmaceutical compns. of **hepatotoxic** compds. are provided in which the **hepatotoxicity** of the compds. is mitigated by including quantities of **nicotinamide** and **methionine** in the composition **Folic acid** also can be included to further mitigate the **hepatotoxic** effects. The **hepatotoxic** compds. can include **acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole**, divalproex sodium, and **valproic acid.**

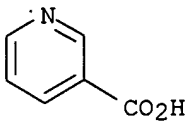
IT **59-05-2, Methotrexate 59-67-6, Niacin**, biological studies **99-66-1, Valproic acid 103-90-2, Acetaminophen 76584-70-8**, Divalproex sodium **79902-63-9, Simvastatin 86386-73-4, Fluconazole 134523-00-5, Atorvastatin**
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. with reduced **hepatotoxicity**)

RN 59-05-2 CAPLUS
CN L-Glutamic acid, N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]- (9CI) (CA INDEX NAME)

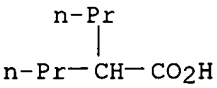
Absolute stereochemistry.



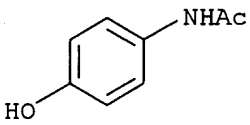
RN 59-67-6 CAPLUS
CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



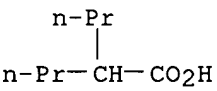
RN 99-66-1 CAPLUS
CN Pentanoic acid, 2-propyl- (9CI) (CA INDEX NAME)



RN 103-90-2 CAPLUS
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



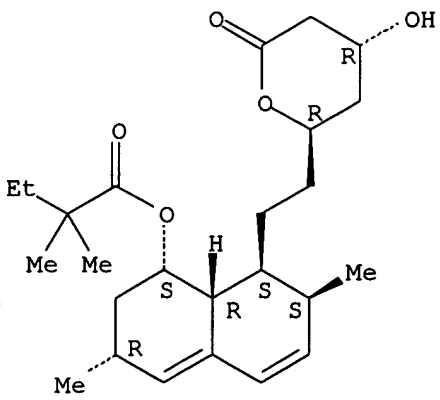
RN 76584-70-8 CAPLUS
CN Pentanoic acid, 2-propyl-, sodium salt (2:1) (9CI) (CA INDEX NAME)



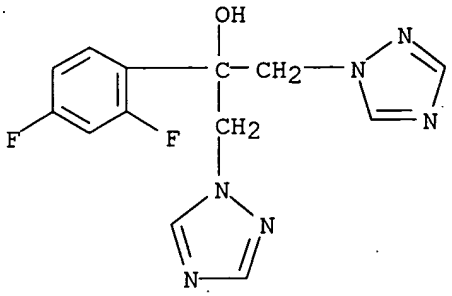
● 1/2 Na

RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

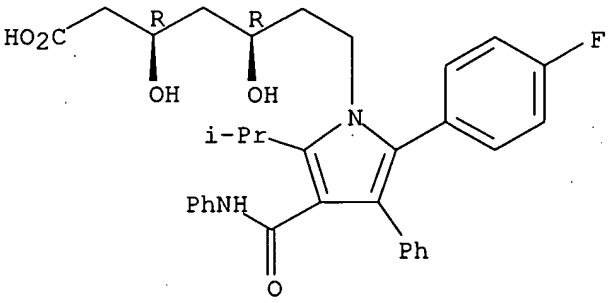


RN 86386-73-4 CAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



RN 134523-00-5 CAPLUS
CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, (βR,δR)-(9CI) (CA INDEX NAME)

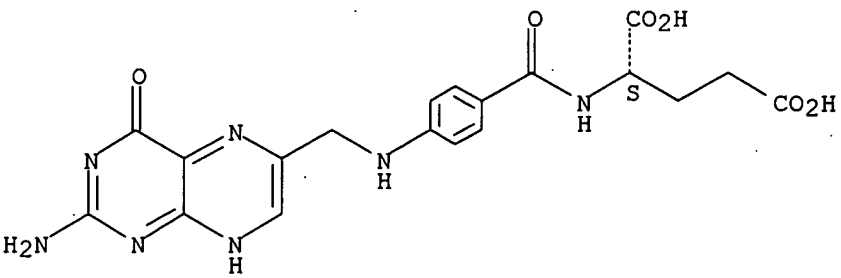
Absolute stereochemistry.



IT **59-30-3, Folic acid**, biological studies
63-68-3, Methionine, biological studies **98-92-0**
, Nicotinamide
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. with reduced **hepatotoxicity**)

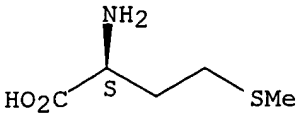
RN 59-30-3 CAPLUS
CN L-Glutamic acid, N-[4-[[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

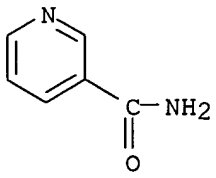


RN 63-68-3 CAPLUS
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 98-92-0 CAPLUS
CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)



L42 ANSWER 2 OF 7 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001398967 EMBASE
TITLE: **Folic acid** revisited.
AUTHOR: Hazra A.; Kumar Tripathi S.
CORPORATE SOURCE: A. Hazra, 17/2/4B Chakraberia Road (South), Calcutta 700025, India. blowfans@cal2.vsnl.net.in
SOURCE: Indian Journal of Pharmacology, (2001) Vol. 33, No. 5, pp. 322-342. .
Refs: 114
ISSN: 0253-7613 CODEN: INJPD2
COUNTRY: India
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index
025 Hematology
020 Gerontology and Geriatrics
021 Developmental Biology and Teratology
036 Health Policy, Economics and Management
005 General Pathology and Pathological Anatomy
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Nov 2001
Last Updated on STN: 30 Nov 2001

AB **Folic acid**, or **pteroylglutamic acid**
, is a well-known water soluble vitamin of the B-complex group. It is necessary for DNA synthesis and normal erythropoiesis. Tetrahydrofolate, the active form of this vitamin, functions as a conenzyme in various metabolic reactions involving transfer of one-carbon moieties. Folate and **vitamin B**(12) metabolic pathways intersect at the conversion of homocysteine to **methionine**. Human beings cannot synthesize this vitamin and must obtain performed folate through dietary sources like green leafy vegetables, cereals, fruits, organ meats and yeast. Synthetic **folic acid** is more bioavailable than food folate. Absorption is predominantly from the upper small intestine and elimination predominantly renal, with modest **hepatic** storage. The daily requirement varies by age and is greater during pregnancy and lactation. Apart from increased demand, folate deficiency

can occur in malnutrition, malabsorption, chronic hemolytic anemias, chronic alcoholism, repeated hemodialysis, and unusual dietary situations like total parenteral nutrition. The use of certain antiepileptic, antimalarial, antimicrobial and anticancer drugs may interfere with the absorption, conversion or utilization of folate leading to megaloblastic anemia. The primary therapeutic indication is in the prophylaxis and treatment of deficiency states. Pharmacological supplementation is recommended in situations like pregnancy (for preventing macrocytic anemia, occurrence or recurrence of neural tube defects, counteracting teratogenic effect of anticonvulsants, etc.), malnutrition, malabsorption and chronic hemodialysis. It may be supplemented during lactation, in infants, the elderly, alcoholics, and in renal failure patients. **Folic acid** may also reduce orofacial clefting and ameliorate **methotrexate toxicity** in rheumatoid arthritis. Pharmacological dose are well-tolerated but folate supplementation aloen in megaloblastic anemia primarily due to **vitamin B**(12) deficiency can worsen the neurological condition. Of late, interest in **folic acid** has grown with the realization that modest folate supplementation can prevent hyperhomocysteinemia, which is an independent graded risk factor for atherosclerotic cardiovascular disease, and is possibly beneficial in certain cancers. The recent stipulation for mandatory folate fortification of cereal products in USA and the inclusion of **folic acid** in the WHO model list of essential drugs recognize the increasing importance of folate in human nutrition. Indeed, **folic acid** has revisited with new therapeutic applications and its mysteries are still unfolding more than 7 decades after its discovery.

L42 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1953:32699 CAPLUS
DOCUMENT NUMBER: 47:32699
ORIGINAL REFERENCE NO.: 47:5557i,5558a-d
TITLE: Pharmacological studies on isonicotinic acid hydrazide
AUTHOR(S): Garattini, S.; Grassi, C.; Mantegazza, P.; Morvillo, V.; Tommasini, R.; Trabucchi, E.
CORPORATE SOURCE: Univ. Milan
SOURCE: Atti della Societa Lombarda di Scienze Mediche e Biologiche (1952), 7(No. Spec.), 1-19;English summary 18-19
CODEN: ASLBAG; ISSN: 0365-690X
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

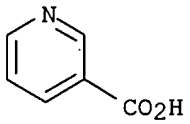
AB Isonicotinic acid hydrazide (I) showed a more intense inhibiting action than streptomycin on Koch's bacilli in vitro. Vitamins B1, B2, and B6, p-aminobenzoic acid, uracil, thymine, **nicotinamide**, choline, **methionine**, **folic acid**, pantothenic acid, isonicotinic acid, and isonicotinamide were inefficient in counteracting I action. (1) p-Aminobenzoic acid hydrazide, nicotinic acid hydrazide, and isonicotinic acid amide, (2) succinic acid bishydrazide, and (3) pyrazincarboxylic acid hydrazide had, resp., (1) no, (2) some, and (3) a considerable inhibiting action on Koch's bacilli. Also in vivo, in rats, the effect of I was higher than that of streptomycin. Intravenously injected I was distributed rapidly to the various tissues, especially to **liver**; exchanges through the blood-tissue barrier occurred in both senses; I urinary excretion occurred within some hrs. after injection. I was rapidly destroyed in the organism (removal of both the terminal N, with formation of NH3 and isonicotinamide, and of the whole hydrazine group with formation of isonicotinic acid). Also in vitro I was decomposed (lateral chain taken off) by slices of **liver**, lung, and brain and by yeasts; this action was inhibited by thiourea and p-aminobenzoic acid. Metabolisms of I and of isonicotinic acid and its amide were different from that of **nicotinamide** since the pyridine N was not alkylated. The nervous phenomena due to I

administration to animals were also investigated: the association of thiourea and p-aminobenzoic acid with I attenuated its convulsive effect, the association of pyruvic acid enhanced the resistance of animals to the **toxic** effects of I. The administration of I lowered the pyruvic acid level of blood in humans and animals (and of the brain of the latter), and in sound subjects caused also a drop of blood eosinophils and in guinea pigs a considerable drop of the ascorbic acid content of adrenal glands (by high I doses).

IT **59-67-6**, Nicotinic acid
(hydrazides, bacteriostatic action on tubercle bacilli)

RN 59-67-6 CAPLUS

CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



L42 ANSWER 4 OF 7 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004257294 EMBASE

TITLE: The effect of fibrates and other lipid-lowering drugs on plasma homocysteine levels.

AUTHOR: Dierkes J.; Westphal S.; Luley C.

CORPORATE SOURCE: Dr. J. Dierkes, Inst. of Clinica Chem./Biochemistry, University Hospital Magdeburg, Leipziger Str. 44, 39120 Magdeburg, Germany. jutta.dierkes@medizin.uni-magdeburg.de

SOURCE: Expert Opinion on Drug Safety, (2004) Vol. 3, No. 2, pp. 101-111. .
Refs: 84
ISSN: 1474-0338 CODEN: EODSA

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 003 Endocrinology
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 1 Jul 2004
Last Updated on STN: 1 Jul 2004

AB Hyperlipidaemia is a major risk factor for cardiovascular disease. The drugs of choice for the treatment of hyperlipidaemia are either fibrates, in the case of hypertriglyceridaemia, or statins, in the case of hypercholesterolaemia. Recently, it has been shown that some of the most prescribed fibrates cause hyperhomocysteinaemia, which itself has been recognised as a cardiovascular risk factor. In particular, fenofibrate and bezafibrate lead to a 20 - 40% elevation of plasma levels of the atherogenic amino acid homocysteine, thereby possibly counteracting the desired cardiovascular protection. The most likely mechanism for this increase is an alteration of creatine-creatinine metabolism and changes in methyl transfer. Gemfibrozil does not increase homocysteine. Statins have no effect on the plasma homocysteine concentration. The increase of plasma homocysteine after fenofibrate can be lowered by the concurrent administration of **folic acid** and **vitamins** **B**(12) and B(6). Thus, patients with hypertriglyceridaemia can either be concurrently treated with fenofibrate and vitamins or with gemfibrozil. 2004 .COPYRGT. Ashley Publications Ltd.

L42 ANSWER 5 OF 7 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 97048562 EMBASE
DOCUMENT NUMBER: 1997048562
TITLE: Male rats fed methyl- and folate-deficient diets with or without **niacin** develop **hepatic** carcinomas associated with decreased tissue NAD concentrations and altered poly(ADP-ribose) polymerase activity.
AUTHOR: Henning S.M.; Swendseid M.E.; Coulson W.F.
CORPORATE SOURCE: S.M. Henning, Community Health Sciences, School of Public Health, University of California, Los Angeles, CA 90095, United States
SOURCE: Journal of Nutrition, (1997) Vol. 127, No. 1, pp. 30-36. . Refs: 26
ISSN: 0022-3166 CODEN: JONUAI
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 10 Mar 1997
Last Updated on STN: 10 Mar 1997

AB Folate is an essential cofactor in the generation of endogenous **methionine**, and there is evidence that folate deficiency exacerbates the effects of a diet low in choline and **methionine**, including alterations in poly(ADP-ribose) polymerase (PARP) activity, an enzyme associated with DNA replication and repair. Because PARP requires NAD as its substrate, we postulated that a deficiency of both folate and **niacin** would enhance the development of **liver** cancer in rats fed a diet deficient in **methionine** and choline. In two experiments, rats were fed choline- and folate-deficient, low **methionine** diets containing either 12 or 8% casein (12% MCFD, 8% MCFD) or 6% casein and 6% gelatin with **niacin** (MCFD) or without **niacin** (MCFND) and were compared with folate-supplemented controls. **Liver** NAD concentrations were lower in all methyl-deficient rats after 2-17 mo. At 17 mo, NAD concentrations in other tissues of rats fed these diets were also lower than in controls. Compared with control values, **liver** PARP activity was enhanced in rats fed the 12% MCFD diet but was lower in MCFND-fed rats following a further reduction in **liver** NAD concentration. These changes in PARP activity associated with lower NAD concentrations may slow DNA repair and enhance DNA **damage**. Only rats fed the MCFD and MCFND diets developed **hepatocarcinomas** after 12-17 mo. In Experiment 2, **hepatocarcinomas** were found in 100% of rats fed the MCFD and MCFND diets. These preliminary results indicate that **folic acid** deficiency enhances tumor development. Because tumors developed in 100% of the MCFD-fed rats and because tissue concentrations of NAD in these animals were also low, further studies are needed to clearly define the role of **niacin** in methyldeficient rats.

L42 ANSWER 6 OF 7 MEDLINE on STN

ACCESSION NUMBER: 2002462179 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12221238
TITLE: Acute valproate administration impairs **methionine** metabolism in rats.
AUTHOR: Ubeda Natalia; Alonso-Aperte Elena; Varela-Moreiras Gregorio
CORPORATE SOURCE: Seccion de Nutricion, Bromatologia y Dietetica, Facultad de Ciencias Experimentales y de la Salud, Universidad San Pablo CEU, Madrid, Spain.. nubeda@ceu.es

SOURCE: The Journal of nutrition, (2002 Sep) Vol. 132, No. 9, pp. 2737-42.
Journal code: 0404243. ISSN: 0022-3166.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 11 Sep 2002
Last Updated on STN: 7 Feb 2003
Entered Medline: 6 Feb 2003

AB Valproate (VPA) is a drug widely used to treat epilepsy, but it has serious adverse effects including **hepatotoxicity**, teratogenicity and antifolate activity. The mechanism underlying VPA **toxicity** is unclear although an interaction with folate and other metabolites involved in **methionine** metabolism has been suggested. The present study was undertaken to evaluate potential changes in the metabolic function of the **methionine** cycle after acute exposure to a single dose of valproate. Female Wistar rats (n = 30) were treated with 400 mg/kg of VPA. Different groups of six rats were killed at 1 (t1), 3 (t3), 6 (t6), 9 (t9), and 24 (t24) hours after the injection. One group of rats was untreated (n = 6) and was considered the control group. The most pronounced effects of VPA administration were observed 1 h after drug injection. VPA induced a 56% reduction in **methionine** adenosyltransferase activity and a 54% reduction in plasma **vitamin B**-6. Increases in the **hepatic** concentration of S-adenosylhomocysteine and oxidized glutathione, and a reduction in the S-adenosylmethionine/S-adenosylhomocysteine transmethylation ratio also occurred at 1 h. All of these alterations, however, were normalized within 24 h, parallel with a decrease in serum VPA concentration. The acute effects of VPA suggest that the alterations in the **methionine** cycle could be the common mechanism underlying the **hepatotoxic**, teratogenic and antifolate effects of the drug.

L42 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:162309 CAPLUS
DOCUMENT NUMBER: 140:205217
TITLE: System for exsanguinous metabolic support of an organ or tissue
INVENTOR(S): Brasile, Lauren
PATENT ASSIGNEE(S): Breonics, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 25 pp., Cont.-in-part of U.S. Ser. No. 849,618.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004038192	A1	20040226	US 2003-443452	20030522
US 6642045	B1	20031104	US 2000-547843	20000412
US 2002012988	A1	20020131	US 2001-849618	20010504
US 6582953	B2	20030624		
US 2004038193	A1	20040226	US 2003-650986	20030827
WO 2004105484	A1	20041209	WO 2004-US16085	20040521

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

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PRIORITY APPLN. INFO.:

US 1999-129257P	P	19990414
US 2000-547843	A2	20000412
US 2001-849618	A2	20010504
WO 2000-US9894	W	20000413
US 2003-443452	A	20030522

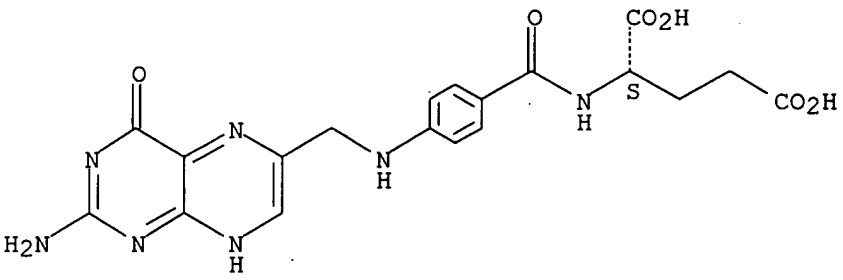
AB An exsanguinous metabolic support system for maintaining an organ or tissue at a near normal metabolic rate is disclosed that employs a warm perfusion solution capable of altering the production of nitric oxide (NO) in an organ or tissue and supporting the metabolism of the organ or tissue at normothermic temps. Perfusion with the solution of the invention can therefore be used to regulate nitric oxide production in situations where it is desirable to do so, e.g. to prevent reperfusion injury. The system also monitors parameters of the circulating perfusion solution, such as pH, temperature, osmolarity, flow rate, vascular pressure and partial pressure of respiratory gases, and nitric oxide (NO) concentration and regulates them to insure that the organ is maintained under near-physiol. conditions. Use of the system for long-term maintenance of organs for transplantation, for resuscitation and repair of organs having sustained warm ischemic **damage**, to treat cardiovascular disorders, to prevent reperfusion injury, as a pharmaceutical delivery system and prognosticator of post-transplantation organ function is also disclosed.

IT **59-30-3, Folic Acid**, biological studies
59-51-8, Methionine 59-67-6, Nicotinic Acid, biological studies **98-92-0, Niacinamide**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(system for exsanguinous metabolic support of an organ or tissue)

RN 59-30-3 CAPLUS

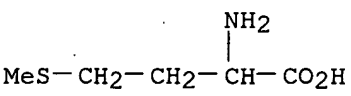
CN L-Glutamic acid, N-[4-[[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



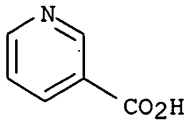
RN 59-51-8 CAPLUS

CN Methionine (9CI) (CA INDEX NAME)

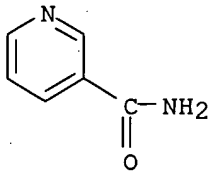


RN 59-67-6 CAPLUS

CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



RN 98-92-0 CAPLUS
CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)



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